ATTACHMENT C

REMARKS

By this amendment, and in accordance with the recent Interview between Applicants' representatives and the Examiner and Supervisor, the Applicants have now provided a new set of claims which reflects the discussions during the Interview and which overcomes all outstanding rejections and now places this application in condition for allowance. In particular, new independent claim 105 which replaces prior claim 50 is directed to a method of treating infertility by inducing immune tolerance to a paternal antigen in a mammalian prospective mother lacking said immune tolerance via exposing a mucosal surface of the prospective mother to (a) semen or MHC Class I antigen of a prospective father capable of eliciting a Th-1 response; and (b) a substantially purified TGFβ selected from the group consisting of TGFβ1, TGFβ2 and TGFβ3; wherein the MHC Class I antigen is one that is present on leukocytes or in seminal plasma of the prospective father, and wherein the exposure is at a time and in an amount effective to induce said immune tolerance. In consideration of the fact that the original specification and claims completely disclose the new set of claims, these claims are thus supported in the original application and no new matter has been added. For reasons as stated below, and as provided in the attached Declaration of Dr. David Alexander Clark, a participant in the Interview with the Examiner and Supervisor, the present set of claims overcome all outstanding rejections and place this case in condition for allowance.

As an initial matter, Applicants wish to acknowledge with appreciation the Interview granted between Applicants' representatives and the Examiner and

Supervisor which, for reasons as stated in detail below, was very helpful in overcoming prior objections and bringing this case towards an allowance.

In the prior Final Rejection, the Examiner had rejected 50-59, 64-71, 79, 81, 83 86-93 and 98-104 under 35 U.S.C § 112, first paragraph, on the ground that the specification, while being enabling for a method of diminishing the DTH immune response, or more particularly eliciting a Th-1 response, through the administration of substantially purified TGFβ for a time and in an amount effective to induce immune tolerance, was not enabled for a variety of reasons. This rejection, insofar as applied to the claims as amended, is respectfully traversed in the new set of claims for at least the following reasons.

As an initial ground of rejection, the Examiner objected to the use of the term "any infertility condition" as set forth in the previous claims, and this objection is overcome in the new claims which do not include this term. In addition, the Examiner objected to the use of the term "sperm antigen" and once again, this objection is overcome in the new claims wherein this term is not employed. Instead, the term "semen" which the Examiner and Supervisor acknowledged in the Interview, was used in the claims. Next, the Examiner argued that the claims were not enabled for the use of TGFβ1, TGFβ2, TGFβ3 and activin, and this objection is firstly overcome by the elimination of the term "activin" from the claims. With regard to the remaining elements of TGFβ1, TGFβ2 and TGFβ3, as was pointed out in the Interview, and as is pointed out in the present and previous Declarations of Dr. David Alexander Clark, a participant in the recent Interview with the Examiner, these three isoforms of TGFβ are clearly

enabled by the present specification and are interchangeable when used in the invention.

In particular, in addition to the information provided previously and acknowledged by the Examiner regarding the TGFβ isoforms β1 and β2, the attached Declaration of Dr. Clark reports the excellent results obtained with regard to the use of TGFβ3 *in vivo,* the results that were reported to the Examiner during the Interview and which were agreed to evidence the successful *in vivo* use of the present invention. As shown in the attached Declaration, an experimental study in accordance with the presently-claimed invention was conducted by Dr. Clark which evaluated the effect of TGFβ3 on the abortion rate in a mouse model of recurrent miscarriage. In these tests, human TGFβ3 significantly reduced the proportion of miscarriage in the CBA x DBA/2 mouse model of recurrent miscarriage, a result which was statistically significant. See attached Clark Dec. at 17-21. Moreover, Dr. Clark further states that these tests provide additional support for the interchangeability of the three TGFβ isoforms. See Clark Dec. at 21. Accordingly, based on the specification and additional supporting materials provided herein and previously by Dr. Clark, and as was acknowledged during the Interview with the Examiner and Supervisor, there is no question that the present invention is enabled with regard to the three TGFβ isoforms as set forth in the amended claims, and any objection on this basis has been respectfully traversed and should be withdrawn.

In the prior Final Rejection, the Examiner had also rejected 50-59, 64-71, 79, 81, 83 86-93 and 98-104 under 35 U.S.C § 112, first paragraph, on the ground that the specification did not provide an adequate written description of the claimed invention. In particular, the Examiner once again referred to the fact that the prior claims referred to

the use of any sperm antigen for any infertility condition. As was discussed in detail during the Interview between Applicants' representatives and the Examiner and Supervisor, the present language of the claims was worked out in such a manner so as to overcome this rejection, namely in that the present claims now refer to a method of treating infertility by inducing immune tolerance to a paternal antigen in a mammalian prospective mother lacking said immune tolerance via exposing a mucosal surface of the prospective mother to semen or MHC Class I antigen of a prospective father wherein said semen or MHC Class I antigen is capable of eliciting a Th-1 response. In addition, the semen or MHC Class 1 antigen as defined in the claims (i.e. the MHC Class I antigen is one which is present on leukocytes or in seminal plasma of the prospective father) are introduced along with a substantially purified TGFβ selected from the group consisting of TGFβ1, TGFβ2 and TGFβ3, and all of these terms are clearly supported in the written description of the present application. Thus, as was acknowledged during the Interview, there is no question that the claims as specifically amended in accordance with the suggestions of the Examiner and Supervisor are fully and adequately described in the specification, and that any remaining objections under 35 U.S.C. § 112 have been traversed and should be withdrawn.

Finally, in the outstanding Final Rejection, the Examiner rejected Claims 50-59, 64-67, 70, 79, 81, 86, 89, 90, 92-93 and 98-104 under 35 U.S.C. § 103(a) as being unpatentable over US Pat. No. 5,395,825 to Feinberg, in view of the Clark et al. December 1994 article and the Chaouat et al. March 1985 article. In addition, other minor rejections were made to prior claims 66-67 and 71, claim 83 and claim 92 on the basis of these three references in combination with other additional references.

However, as was discussed during the Interview between Applicants' representatives and the Examiner and Supervisor, the present invention, as particularly embodied in the new set of claims submitted herewith, is not disclosed or suggested in the prior art which, as discussed further below, actually *teaches away* from the present invention. Moreover, as pointed out in the Interview, and as reflected in the attached Declaration of Dr. Clark, the present invention has obtained unexpected beneficial results beyond what would have been the expectations of the prior art, and thus the invention as presently claimed is clearly unobvious over the cited references, taken either singly or in combination.

In the first place, as set forth in detail during the Interview, the main reference cited by the Examiner, Feinberg US patent 5,395,825, clearly does not disclose or suggest the main element of the present claims, namely a method of treating infertility by inducing specific immune tolerance to a paternal antigen in a mammalian prospective mother *lacking said immune tolerance*. To the contrary, as set forth at the Interview and in the attached Declaration of Dr. Clark, the focus of the Feinberg patent was developing methods for achieving *improved implantation*, and thus there is clearly no disclosure or suggestion of practicing the present method on a mammalian prospective mother *lacking said immune tolerance* which is now part of the present set of amended claims. In other words, as presently claimed, the present method is directed to a specific set of conditions in the mammalian prospective mother which is not disclosed or suggested in the Feinberg patent, and thus the Feinberg patent does not disclose or suggest *at all* achieving an induction of immune tolerance in a mammalian prospective mother lacking such immune tolerance, much less in an amount effective to achieve

such ends. It is thus clear that the Feinberg patent does not disclose or suggest the presently claimed invention, nor are there any other teachings in the other references which could be combined with Feinberg to anticipate or make obvious the present claims.

With regard to the remaining references cited by the Examiner, Dr. Clark's 1994 article and the Chaouat 1995 article, not only do these articles not disclose or suggest the presently claimed invention, for reasons as pointed out in the Interview and in the attached Declaration, the state of the prior art at the time of the present invention actually *taught away* from the invention, so that one of ordinary skill in this art would *not* have thought that the present method would achieve its desired result. In particular, as pointed out in great detail in the attached Declaration, it would have in fact been expected that administering TGF-β to a prospective mother, either before or after attempted conception, would *cause* miscarriage. See Clark Dec., 3-14. Indeed, the disclosures in the prior art specifically *taught away* from the suggestion that MHC Class I antigens might be useful in eliciting protection against abortion and further *taught away* from the suggestion that administration of TGFβ would elicit protection against abortion. Instead, to the contrary, the prior art actually would have predicted to one skilled in the art at the time of invention that administration of TGFβ to a prospective mother, either before or after attempted conception, would *actually have caused miscarriage.* See Clark Dec., 3-14.

Accordingly, there clearly would have been no motivation for a person of ordinary skill in the art to have combined the teachings of Feinberg, Clark or Chaouat to come up with the present invention, because one skilled in the art would not have expected such

a combination to achieve a successful result with regard to treating infertility; in fact, a contrary result would have been expected. On this basis alone, it is clear that the claims as presently amended are not disclosed or suggested by the Feinberg, Clark or Chaouat references, either singly or in combination, and that one skilled in the art would clearly not have arrived at the present invention on the basis of these references and the teachings at the time of the invention.

Even further, as explained in detail at the Interview, and as reflected in the attached Declaration, the present invention has achieved unexpected beneficial results, namely the successful achievement of an induction of immune tolerance so as to treat infertility in a manner not taught or remotely suggested in the prior art. In particular, as reflected in paragraphs 17-21 of the attached Clark declaration, in an experimental study used to evaluate the performance of TGFβ treatment in accordance with the present invention, TGFβ3 was used in an *in vivo* test to assess the effect of TGFβ on the abortion rate in a well-recognized mouse model of recurrent miscarriage. In these tests, a single dose of TGFβ3 administered to a prospective mother lacking immune tolerance to a paternal antigen, either before or after attempted conception, actually *prevented* miscarriage. These results confirm that the claimed invention provides an unexpected beneficial result when compared to what would have been expected based on the teachings of the prior art, and further confirms the non-obviousness and patentability of the present invention.

In the light of the foregoing, it is clear that the invention as presently claimed is not disclosed or suggested by the cited prior art references, and that indeed, one skilled in this art would **not** have been motivated to combine these references in a manner so

as to produce the present invention because the prior art actually **taught away** from making such a combination. Moreover, the invention further provides unexpected beneficial results that would not have been foreseen by the skilled artisan, which provides even further evidence of the patentability of the present invention. In short, none of the cited references, either singly or in combination, disclose or suggest the specific features of Applicants' claimed invention, as particularly embodied in the amended set of new claims, and the Examiner's prior rejections based on the prior art are respectfully traversed and should be withdrawn.

In the light of the above amendments and arguments, as well as the discussions during the recent Interview, and the attached Declaration of Dr. David Alexander Clark, Applicants submit that the present application overcomes all prior rejections and has been placed in condition for allowance. Such action is earnestly solicited.

END REMARKS